Relative effectiveness of cell-cultured versus egg-based influenza vaccines, 2017-18

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Disclaimer

The findings and conclusions in this presentation are those of the authors and do not necessarily represent the official position of FDA, CMS, ACUMEN or any other organization

Background

A CDC-sponsored interim analysis of the A(H3N2)-dominated 2017-18 influenza season showed a low (18%) vaccine effectiveness (VE) among individuals ages ≥65 years in the U.S.

One hypothesis is that egg-adaptation led to lower VE during 2017-18, so we studied the relative effectiveness of inactivated influenza vaccines prepared in mammalian cells (cell-cultured) versus embryonated chicken eggs (egg-based) among Medicare beneficiaries ages ≥65 years

Methods

OBSERVATION PERIOD

August 6, 2017 to April 20, 2018

EXPOSURES

Cell-cultured quadrivalent

Egg-based quadrivalent

Egg-based high-dose trivalent

Egg-based adjuvanted

Egg-based standard-dose trivalent

POPULATION

Medicare Fee-for-service beneficiaries who received the cell-cultured or any of four egg-based influenza vaccinations

OUTCOMES

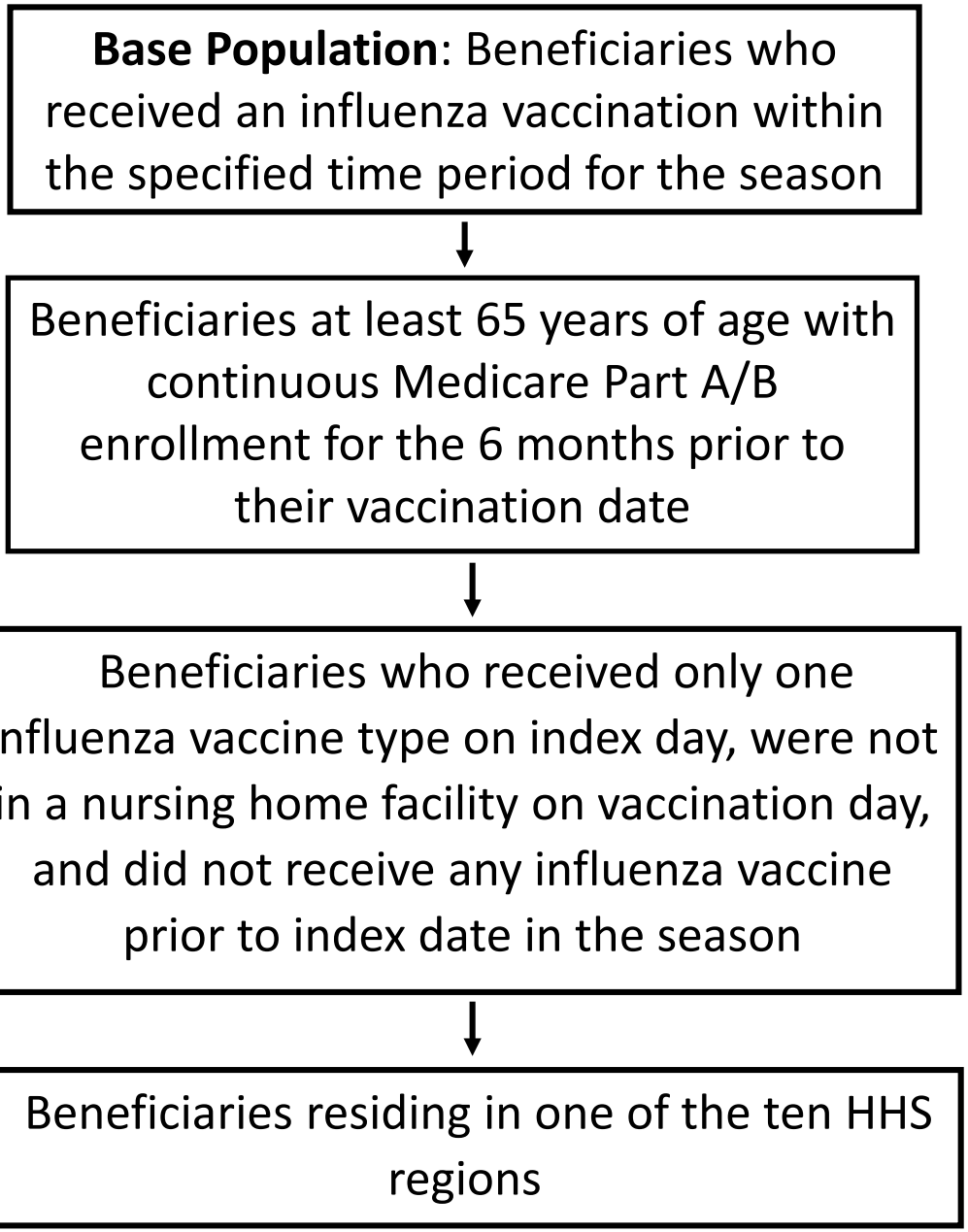
Primary: Influenza hospital encounters (inpatient + ER)

Secondary: Office Visit (RIT + antiviral)

Post-hoc: Inpatient only

All during high circulation periods

Selection Process for Beneficiaries Included in the Study



Final Study Populations

Cell-Cultured Quadrivalent (ccIIV4):	**N= 653,099**
Egg-Based Quadrivalent (IIV4):	**N= 1,844,745**
Egg-Based High-Dose Trivalent (IIV3-HD):	**N= 8,449,508**
Egg-Based Adjuvanted (aIIV3):	**N= 1,465,747**
Egg-Based Standard-Dose Trivalent (IIV3):	**N= 1,007,082**

Covariate Balance

- We used standardized mean differences (SMDs) to determine cohort balance for 62 covariates
- Approximately half of the 62 demographics and health utilization covariates were initially imbalanced
- Stabilized inverse probability of treatment weighting (IPTW) was used to address imbalance in all measured covariates
- Following IPTW, cohort balance was achieved with SMDs <0.05 for all covariates

Selected (Imbalanced) Covariates

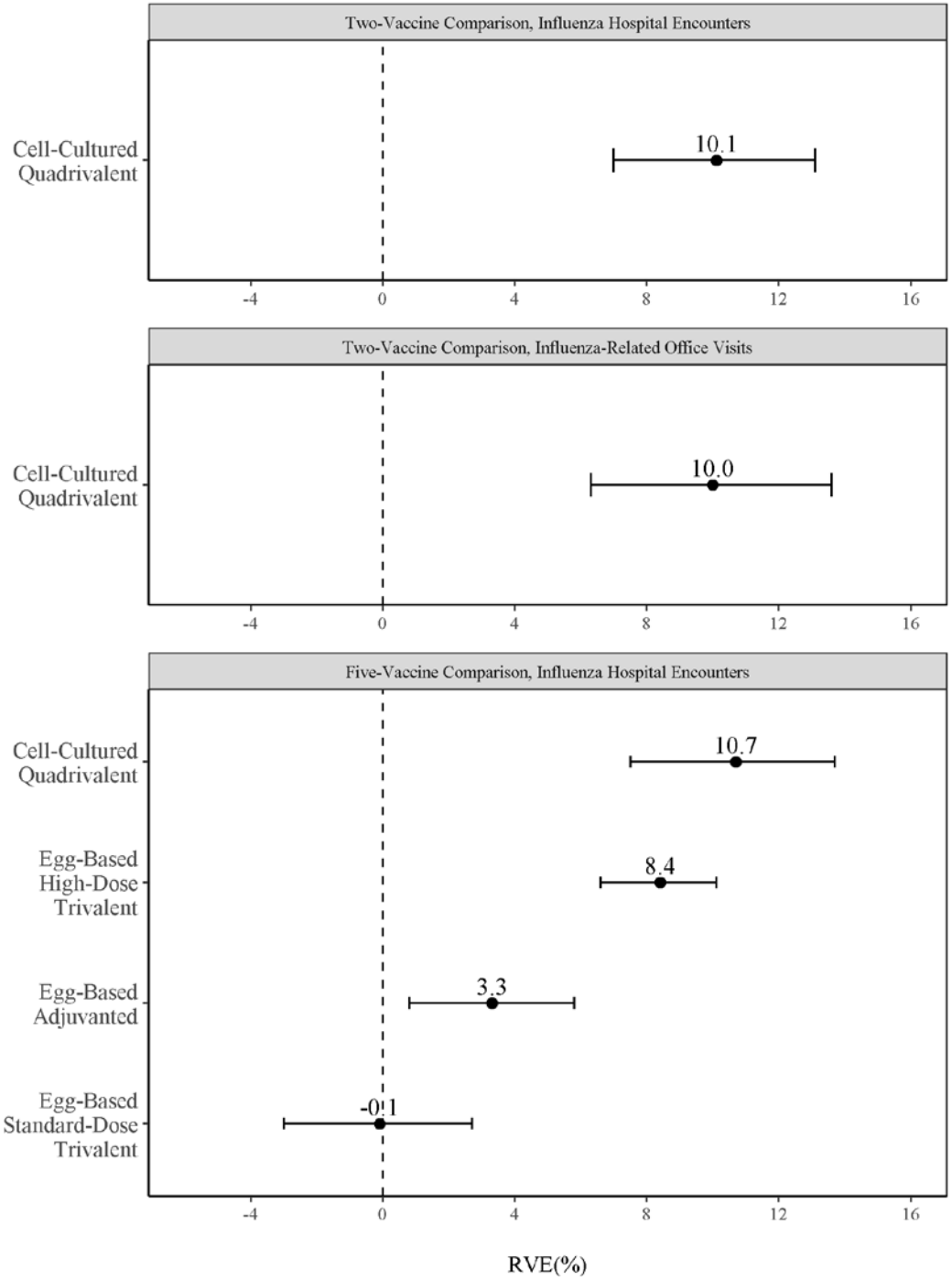
Covariates	ccIIV4	IIV4	IIV3-HD	aIIV3	IIV3	*Pre-Weight Max SMD*	*Post-Weight Max SMD*
Vaccinated at Pharmacy	19.2%	9.2%	**44.4%**	**67.5%**	11.7%	1.39	0.03
Dual Eligible	13.3%	11.3%	6.9%	6.8%	**16.3%**	0.22	0.05
Month of Vaccination: August & September	27.4%	26.1%	**33.6%**	**30.9%**	22.6%	0.25	0.03
No Prior Outpatient Non-ER Visits	**43.5%**	32.2%	36.9%	40.4%	37.5%	0.14	0.02

Addressing Potential Sources of Bias

- Used IPTW to address imbalance in all measured covariates
- IPTW did not necessarily address imbalance for unmeasured potential confounders, an issue often found when real world data are used
- IPTW adjusted relative vaccine effectiveness (RVE) was obtained using univariate Poisson regression

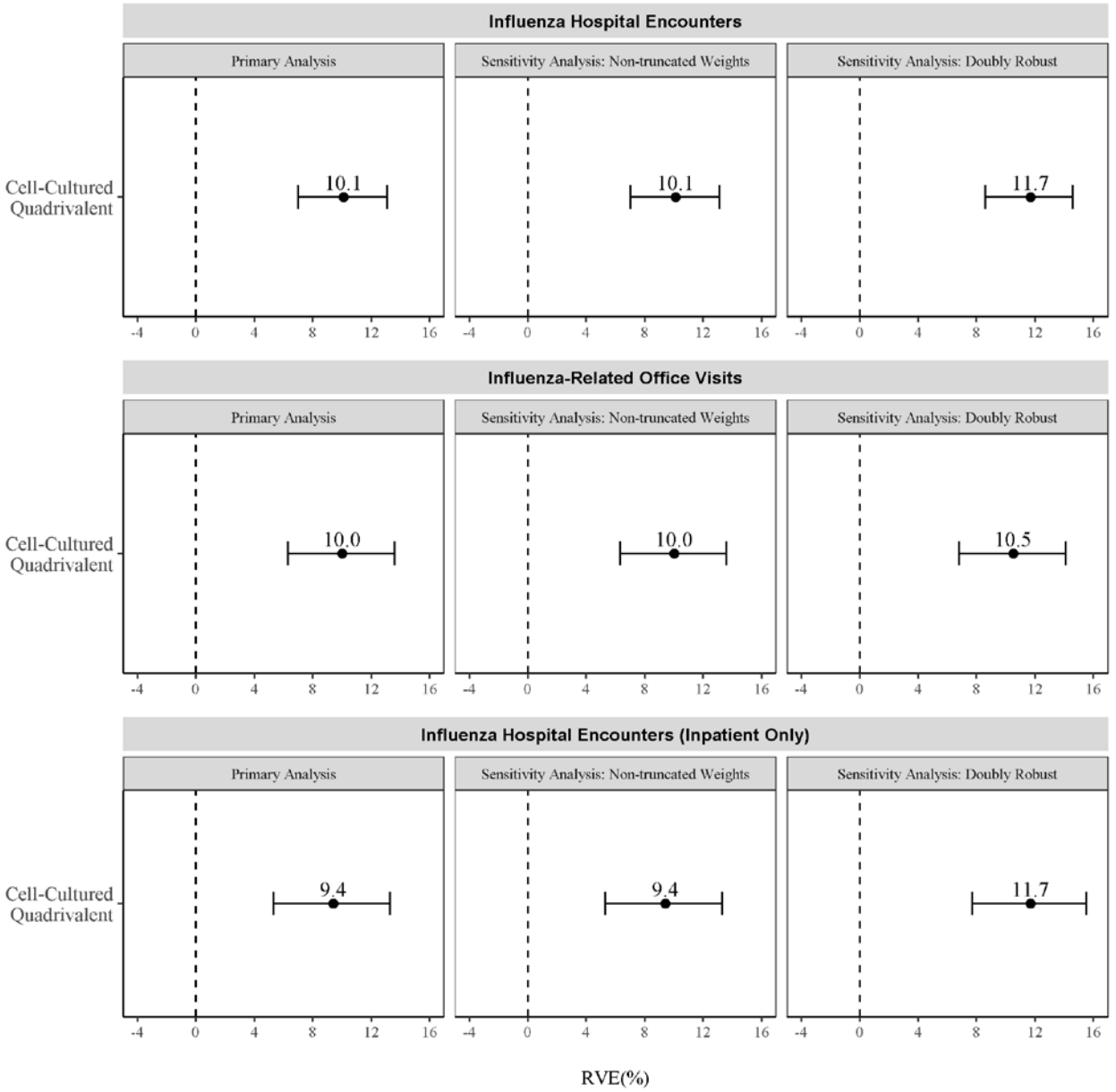
IPTW Adjusted Poisson Regression RVE: Two and Five-Vaccine Comparisons

(Egg-Based Quadrivalent Vaccine Cohort as Reference)



IPTW Adjusted RVE: Two-Vaccine Comparison Sensitivity Analysis

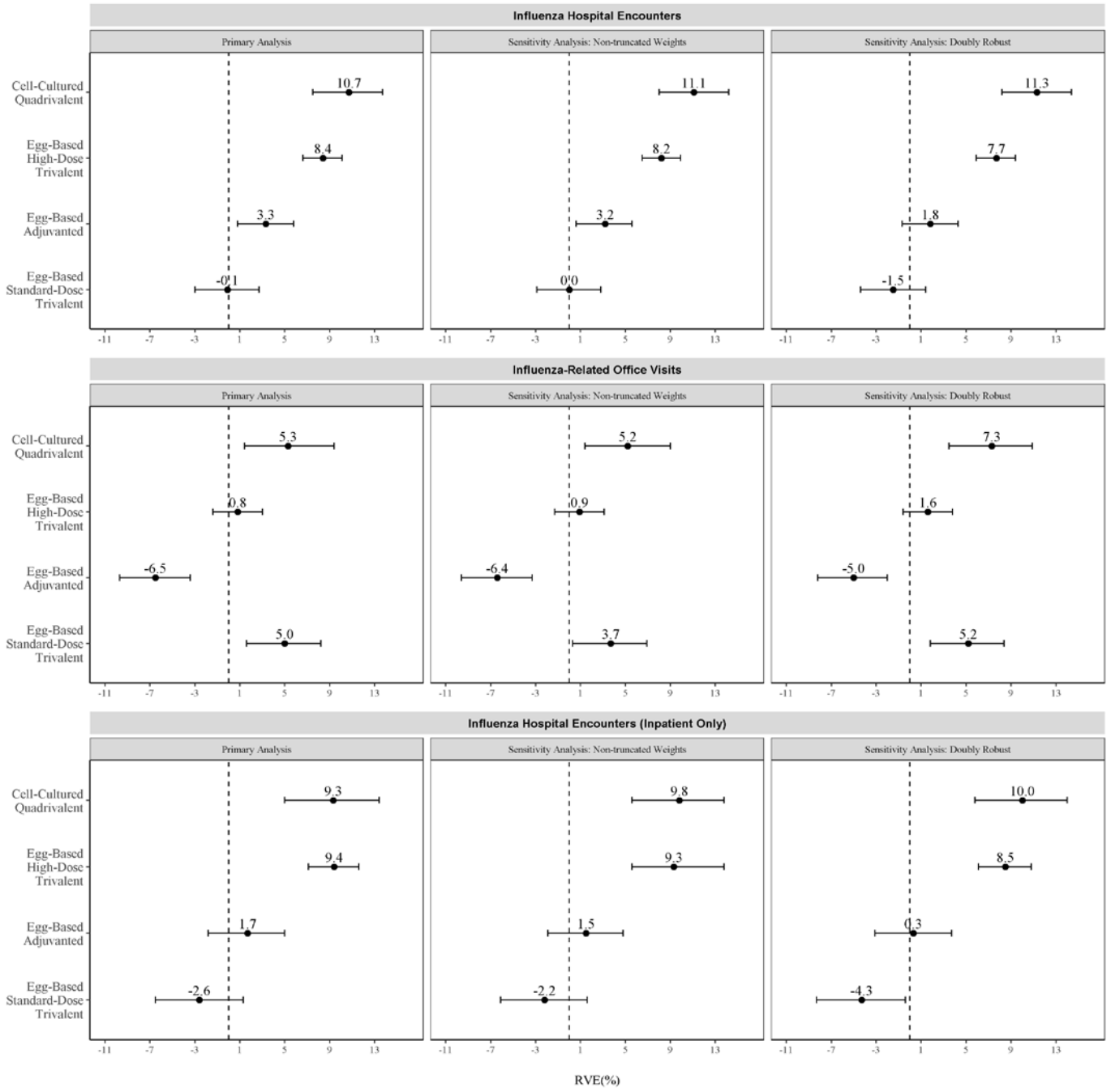
(Egg-Based Quadrivalent Vaccine Cohort as Reference)



IPTW Adjusted RVE:

Five-Vaccine Comparison, Sensitivity Analysis

(Egg-Based Quadrivalent Vaccine Cohort as Reference)



Strengths

- These real world data include nearly all of the actual vaccine recipients ages 65+ nationally
- Data reflect the exposure and outcome experiences during routine clinical practice
- Unlike clinical trials, Medicare beneficiaries have a wider range of health conditions
- Large dataset provides power to detect small but clinically relevant differences and analyze rare serious outcomes

Limitations

- Real world data "are not collected or organized with the goal of supporting research, nor have they typically been optimized for such purposes"†
- Potential exposure and outcome misclassification
- Potential unmeasured confounding even after adjusting for measured covariates
- Influenza-related office visit results were inconsistent
- No virologic case confirmation, and can not differentiate between A(H3N2), A(H1N1), or B infections
- Processing delay for exposure and outcome codes

†N Engl J Med 2016; 375:2293-2297 DOI: 10.1056/NEJMsb1609216

Summary 1

- In this analysis, the cell-cultured and high-dose vaccines were marginally more effective than the egg-based quadrivalent vaccines for hospital outcomes among U.S. people 65+ years during the 2017-18 season
  - Cell-cultured vaccines were 10.7% (95% CI 7.5, 13.7) more effective
  - High-dose vaccines were 8.4% (95% CI 6.6, 10.1) more effective
- These findings contribute to a growing evidence base about new and enhanced vaccines compared to traditional vaccines
  - This is the first comparison of several new and enhanced vaccines to both egg-based traditional vaccines and to each other
  - We will continue to monitor RVE for additional seasons

Summary 2

- Findings from this single observational study should be considered as part of the entire body of evidence
- While cell-cultured and high-dose influenza vaccines appear to offer some additional benefit to older adults, further efforts are needed to improve influenza vaccine effectiveness
- RVE could vary from season to season, data from more seasons are needed
- The results from similar studies conducted in different settings or health systems would provide important context for our results
- We continue to investigate ways to minimize and quantify potential sources of bias in real world evidence studies

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